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EXAMINER	
NOBLE, MARCIA STEPHENS	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/642,272	HATTORI ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *15-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☒ Claim(s) *1 and 2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/4/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-14 with a species election of chronic heart failure for claims 7 and 14 in the reply filed on 6/13/06 is acknowledged. The traversal is on the ground(s) that the restriction groups refer to distinct subject matter but they would not be a search burden because many of the groups pertain to the same subject matter and are classified together. This is not found persuasive because the search strategy would differ between the groups even though some of the groups are classified together. Because of the significant reliance upon the non-patent literature in examination of the biotechnology art, applications are rarely searched by classification and are more commonly searched by terminology, therefore search burden is based upon additional or different terms that must be added to the search query. In the instant case, additional terms such as diagnostic, expression levels, transgenic transformed tissue, as well as all the different species of claims 7 and 14 would need to be search in several different databases, therefore resulting in multiple additional searches. This level of additional search is consider undue and would be considered a search burden for the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement

in the reply filed on 6/13/06. Claims 1-32 are pending and claims 1-14 are under consideration in the instant office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) filed after the mailing date of on 12/4/03. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. However, Foreign Patent Documents, EP 967207 A1 and WO 95/04041 A1, on Sheet 1 of the IDS were not considered because it was in a language other than English and therefore was crossed out.

The information disclosure statement filed 12/4/03 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The examiner was able to retrieve and consider the U.S. patents and WO documents listed, but copies of the non-patent literature documents could not be located. Reference P4 on Sheet 1 and P5 on Sheet 2 were not provided by Applicant, and therefore they were not considered.

Sequence Compliance

3. The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

Page 37, line 1 of the specification recites an amino acid sequence that does not have a SEQ ID NO: that corresponds to the CRF and Sequence Listing.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Specification

4. The use of the trademark Taqman® on p. 38, [00123] and p. 46, [00141], and THERMO Sequences™, on p. 39, [00126], has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

5. Claims 1 and 2 are objected to because of the following informalities: Claims 1 and 2 recite, "transfecting a nucleic acid". However, nucleic acids are not transfected. Cells are transfected with nucleic acids.

Claim 1 is further objected to for not reciting what is being transfected with a nucleic acid (eg- a cell, a mouse, a human, etc...).

Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

6. Claim 14 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 8. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 14 specifies the intended disease to be treated by the prophylactic or therapeutic agent. However, the composition of the agent remains the same as the

agent of claim 8, and therefore, is a duplicate of claim 8. The scope of claim 14 does not appear to differ from that of claim 8.

7. Claim 7 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 7 specifies the intended disease to be treated by the prophylactic or therapeutic method. However, the method steps of claim 7 remains the same as the method steps of claim 1, and therefore, is a duplicate of claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

7. Claim(s) 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to a method for treating chronic heart failure comprising: (1) transfecting cell of an affected tissue with a nucleic acid encoding AOP-1 or a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 or (2) administering a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1. The instant invention is also drawn to a prophylactic or therapeutic agent comprising (1) a nucleic acid encoding AOP-1 or a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 or (2) a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1.

When the claims are analyzed in light of the specification, the instant invention encompasses a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compared with the amino acid sequence of AOP-1 while retaining the function of AOP1 and also encompasses a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1. However, the specification only discloses a nucleic acid encoding AOP-1. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. While the specification mentions prophetically a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compared with the amino acid sequence of AOP-1 while retaining the

function of AOP1 and a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1, the specification fails to disclose any nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compared with the amino acid sequence of AOP-1 while retaining the function of AOP1 and fails to disclose any material that enhances AOP-1 expression, production, or function other than AOP-1 itself. Therefore because the specification only discloses one species, a nucleic acid encoding AOP1, the specification does not teach the complete structure of a representative number of species of the claimed genus that comprises a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant characteristics, specified features and functional attributes that would distinguish different members of the claimed genus. The specification describes that AOP-1 has the same nucleic acid sequence as MER-5 and peroxiredoxin 3 (p. 5, [0010]). The specification also describes that materials having the effect of enhancing of the expression of the AOP-1 gene, the production of AOP-1, or the function of AOP-1 may be synthesized or genetically engineered compounds or natural compounds or derivatives thereof (p. 24, [0084] and[0085] and p. 25 [0087]). However, this does not specifically disclose any special identifying features/characteristics that would distinguish the species of the genus comprising a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compared with the amino acid sequence of AOP-1 while

retaining the function of AOP-1 or the genus comprising a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1. Therefore, a representative number of species have not been sufficiently described by other relevant characteristics, specified features and functional attributes in the specification as required by the written description requirement.

In conclusion, given the breadth of the genus, species have not been sufficiently described by other relevant characteristics, specified features and functional attributes, and the limited number of examples provided, and given that no specific identifying features/characteristic of species of the genus, were provided, the written description requirement disclosing the complete structure of genus comprising a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compared with the amino acid sequence of AOP-1 while retaining the function of AOP1 or the genus comprising a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1 has not been met. Furthermore, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the genus comprising a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compared with the amino acid sequence of AOP-1 while retaining the function of AOP1 or the genus comprising a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1, at the time the application was filed.

Scope of Enablement

8. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating chronic heart failure comprising administering to the heart of a rodent by direct cardiac injection or catheter-based delivery, a vector comprising a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said nucleic acid encoding AOP-1 in the heart of said rodent and while being enabling for a therapeutic agent for treatment of chronic heart failure comprising a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said AOP-1 nucleic acid in the heart and wherein said nucleic acid enhances the expression and production of AOP-1, does not reasonably provide enablement for a prophylactic or therapeutic agent for a disease associated with decreased AOP-1 gene expression comprising: (1) transfecting cell of any affected tissue with any nucleic acid encoding AOP-1 or a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 by any means of delivery or (2) administering a material enhancing the expression of an/the AOP-1 gene, the production of AOP-1, or the function of AOP-1 by any means of delivery and does not reasonably enable a prophylactic or therapeutic agent for any disease associated with decreased expression of AOP-1 gene or AOP-1, comprising (1) any nucleic acid encoding AOP-1 or (2) any material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use or make the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification discloses the purpose of the instant invention is to provide methods of preventing or treating diseases associated with decreased expression of AOP-1 gene or protein (p. 6, [0011]). The specification provides in vitro evidence that that cardiac myocytes transfected with AOP-1 are provided protection by AOP-1 against damage and loss of cell viability induced by hypoxia and reperfusion following hypoxia

(p. 41-42, [00132]). The specification also provides a method of delivering an adenoviral vector encoding a AOP-1 gene, operably linked to a CMV promoter and a poly A signal from bovine growth hormone (p. 40, [00127]), to the left ventricle of the heart via a catheter in a chronic hear disease rodent model (p. 48, [00151]). AOP-1 gene delivery to the heart resulted in significantly better functional recovery during reperfusion following induced ischemic attach. The time from ischemia to ischemic rigidity was significantly extended in the AOP-1 treated heart compared to sham controls. Also, LDH release, a marker correlated with cell injury and necrosis, was significantly repressed in the AOP-1 treated group compared to controls (p. 49, [00153]).

The art teaches that in vivo cardiac gene delivery to rodents is feasible by direct injection or catheter-based delivery using viral vectors (Hajjar et al PNAS 95:5251-5226, 1998) and also demonstrated its use in cardiac disease and heart failure rodent models (del Monte et al. Circulation 104:1424-1429, 2001). However, at the time of filing, the art of gene therapy for cardiac disease was premature for clinical use and many obstacles would need to be overcome before human trials were possible (Hajjar et al. Circ Res 86:616-621, 2000).

Tomasoni and Benigni (Current Gene Therapy 4: 115, col 1 lines 4-7) state, "the success of gene therapy largely depends on an efficient delivery system for the transfer and expression of the therapeutic gene in the target organ or tissue." Many forms of vector delivery to a body site have been described in the art, but very few predictably deliver a therapeutic dose of a vector to the site of treatment. Gautam et al (Am J

Respir Med, 1(1) abstract) discloses the use of different vector delivery routes to the lung, such as intravenous injection, intratracheal installation, and aerosol with varying degrees of success. They further disclose various barriers to delivery of vectors such as serum proteins during intravenous injection, surfactant and mucus interference during more topical applications of vectors. There has also been the problem of immune and cytokine responses against the vector delivery vehicle obstructing delivery of gene therapies. Adenoviral vectors have been problematic in their use for gene therapy due to their immunogenic properties and natural tropism for hepatocytes (Gunther et al, Curr Med Chem – Anti-Cancer Agents, 5:p. 157, col 2, par 2, lines 14-17 to p. 158, col1 par 1, lines 1-3). Therefore, these problematic factors of immune response and alternative tropisms of the vectors preclude the delivery of these vectors by other means than direct administration to the target site.

In terms of specific delivery to the heart, Hajjar et al teaches, "...the vector must be delivered to the affected tissues. This poses a particularly formidable barrier in conditions with an extensively distributed phenotype [p. 617, col 1, par 2, lines 11-14]...direct injection of adenovirus into the ventricular wall using an epicardial approach has also been shown to include significant expression of reporter constructs, however, the expression was focal, and the injections with the myocardium caused needle damage. Intramyocardial delivery of adenovirus using an intraventricular approach with retroinfusion of the coronary veins has also been used in larger animals yielding regional areas of transduction. In rodents, injection of an adenovirus carrying β-galactosidase into the pericardial sac transduced only the pericardial cell layers....[p.

617 bridging cols 1 and 2]." Overall, Hajjar et al suggests that the various approaches to delivering gene to the heart are limited in the efficacy.

The specification discloses a method of catheter-based delivery of the AOP-1 gene vector to the heart of a rat previously disclosed by del Monte et al (2001) (p. 48, [00151]). The specification also provides art of del Monte et al for more specific guidance to the methodology of a catheter-based gene delivery to the heart, therefore, providing enablement for a direct delivery to the cells of the heart by a catheter based delivery system in rat.

However, the instantly claimed invention is drawn to a gene therapy delivered by any method, and given the art described problems associated with the delivery of a vector to a target site by any other means than direct delivery, an artisan would look to the specification to overcome the art described obstacles. The specification only provides specific guidance to a method of direct delivery to the heart via a catheter based system, therefore an artisan would not know how to use or make the instant method utilizing any other means to deliver the vector. Furthermore, for an artisan to carry out the claimed method they would have to determine means of overcoming the unpredictabilities described in the delivery of a vector by means other than the use of direct delivery and this would result in undue experimentation.

The instant invention is drawn to a method of administering an agent that encompasses a nucleic acid encoding AOP-1. However, for a gene therapy agent to be expressed effectively it must minimally comprise the elements to be directed by the transcription and translation machinery of the target cell which require a promoter

capable of driving expression in the target cell. In the instant case, the specification discloses an adenoviral vector comprising the coding sequence for the AOP-1 gene operably linked to the CMV promoter and flanked on the 3' end of the AOP-1 gene a PolyA signal peptide. These elements resulted in the expression of AOP-1 in the heart when directly delivery to the heart. However, the instant claims only disclose "a nucleic acid encoding AOP-1". Because of the necessity for the minimal elements necessary to drive expression of a gene, an artisan would not know how to use a nucleic acid encoding AOP-1 without operable linkage to a promoter, in a gene therapy method that would result in the expression of the therapeutic gene. Furthermore, the claims are drawn to a prophylactic or therapeutic agent nucleic acid encoding AOP-1 (claims 8-14). However, again, an artisan would not know how to use the instant nucleic acid agent for its therapeutic use for the above described reasons.

The instant invention is drawn to the method of administering and agent that encompasses a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1. However, the specification and the art do not teach the elements of the nucleic acid sequence that are necessary to assure the expression of functional AOP-1. Therefore, an artisan would not know how to make a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 without have the design a significant number of

sequence permutation, expressing the different variants, and then determine if they are functional. This level of experimentation would be considered undue.

The instant invention is drawn to the method of administering and agent that encompasses a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1. However, the specification does not teach any material with enhancing properties to the expression of the AOP-1 gene other than an exogenously introduced AOP-1 gene. Therefore, an artisan would not know how to make a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1 with out having to develop test systems that would first identify potential candidate materials for enhancing the expression, production, and function of AOP-1 and the further testing in vitro and in vivo to determine if the candidates actually enhance expression, production, and function of AOP-1. This level of experimentation would be considered undue.

The specification provides an effective use of an adenoviral vector delivery system to a rodent model of cardiac disease. The specification details several art accepted rodent models for cardiac disease. Hajjar et al also demonstrate delivery of a viral vector to the heart of healthy rodents (1998, 2000 and del Monte et al 2001). However, Hajjar et al also teaches, "Early proof of concept experiments in rodents will need to be extended to large-animal models with clinical-grade vectors and delivery systems to assess both efficacy and safety [p. 620, col 2, lines 5-7]." Hajjar et al also teaches that a catheter-based delivery of a viral vector to the rabbit heart in vivo using a method similar to their techniques resulted in less effective delivery of the vector to the

heart and achieved predominantly epicardial transgene expression. [p. 617, col 2, lines 36-38]. Hajjar et al further teach, "Correlates of this method [their rodent catheter-bases delivery of a viral vector to the heart] in humans have not been established...Optimizing conditions for gene transfer in large animals and eventually humans will require substantial further investigation [p. 617, col 2, lines 44-45 and 48-50]". Hajjar et al also teach that the commonly used viral vectors in rodent models result in robust immune responses and therefore will likely require other vectors or further refined adenoviral systems for clinical application (p. 617, col1, par 2, lines 5-8). The problematic use of adenoviral vectors in humans is further supported by Chirmule et al (Gene Therapy, 6:1574-1583, 1999) who teach, "Most of this work [adenoviral gene therapy delivery] has been performed in animal models who are naïve to the virus. This will not be the case in humans, many of whom have been exposed to Ad or AAV due to a naturally acquired infection [p. 1577, sentence bridging col 1 and 2]".

Since the methods of the instant invention are based on the methods of Hajjar et al, and Hajjar et al suggests that these methods are unpredictable in other species besides rodents, the instant invention is also subject to these unpredictabilities. The specification does not provide further guidance to overcome the obstacles described by Hajjar et al. and others in the art; therefore an artisan would not know how to overcome the obstacles and unknowns described in the gene therapy art for any other species than rodent models. Furthermore, for an artisan to use or make the instant invention in any other in vivo model than rodents models, an artisan would have to test other vectors to determine is they are effective for delivery to cells in vitro, then determine if they are

effective in transfecting cells in vivo, and then at least in the case of human, determine if the vector is safe for clinical use. This level of empirical experimentation goes beyond the bounds of routine experimentation and therefore considered undue.

The breadth of claims 1-14 includes prophylactic methods and agents, which encompasses treatment of a subject wherein the subject does not exhibit a disease state to prevent the onset of the disease state. The specification is not enabling for identifying a compound that prevents a condition because prevention or prophylaxis requires that the disease state be stopped before it has begun. The specification does not teach how to assess whether a subject will definitively acquire a condition of chronic heart failure prior to the subject exhibiting symptoms. Once a subject exhibits a phenotype, the methods encompassed by the claims would meet the qualifications for treatment, but not prevention. There are no teachings or guidance in the specification with regard to which subjects would be at risk for developing a phenotype such that the phenotype can be inhibited prior to its onset or at what stage the claimed methods would be carried out to prevent onset of the phenotype.

Overall, the art of effective vector delivery to the heart, as disclosed above, is unpredictable. Therefore, an artisan would look to the specification to provide specific guidance to overcome these obstacles described in the art. The only specific guidance to overcome such obstacles of gene delivery provided are in reference to the method of Hajjar et al 2001. Therefore, an artisan would only know how to effective deliver a vector to the heart by the direct or catheter-based method described in the specification

and art of Hajjar et al, therefore the instant invention is only enable for such disclosed methods of vector delivery to the heart.

Therefore, given the unpredictabilities in the art and the limited guidance provided by the specification, the specification only enables a method of treating chronic heart failure comprising administering to the heart of a rodent by direct cardiac injection or catheter-based delivery a vector comprising a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said nucleic acid encoding AOP-1 in the heart of said rodent and while being enabling for a therapeutic agent for treatment of chronic heart failure comprising an active ingredient of a nucleic acid encoding AOP-1 operably linked to a promoter capable of driving expression of said AOP-1 nucleic acid in the heart and wherein said nucleic acid enhances the expression and production of AOP-1, does not reasonably provide enablement for a prophylactic or therapeutic agent for a disease associated with decreased AOP-1 gene expression comprising: (1) transfecting cell of any affected tissue with any nucleic acid encoding AOP-1 or a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 by any means of delivery or (2) administering a material enhancing the expression of an/the AOP-1 gene, the production of AOP-1, or the function of AOP-1 by any means of delivery and does not reasonably enable a prophylactic or therapeutic agent for any disease associated with decreased expression of AOP-1 gene or AOP-1, comprising (1) any nucleic acid encoding AOP-1 or (2) any

material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-7 and 9-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is incomplete because the method steps do not clearly relate back to the preamble in a positive stem. The claim fails to set forth what is indicative of a therapeutic effect. In other words, claim 1 is drawn to a method comprising "transfecting" or "administering". However, the claim does not disclose to what or whom the nucleic acid will be transfected or administered. Therefore the metes and bound of the instant claim are vague and indefinite.

Claims 2-7 are directly or indirectly dependent upon claim 1. Since claim 1 has been deem indefinite, the dependent claims 2-7 are also rendered indefinite.

Claim 2 recites "while **retaining** the function of AOP-1 **into** cells". "Into" suggests that the function is being added to the cell. However, "retaining suggests that the function was already present in the cell. Therefore, the meets and bounds of this phrase and claim are vague and indefinite.

Claims 3, 4, and 6 recite, "further comprising administering". Claim 1, from which claims 3, 4, and 6 depend, recites "transfecting and administering", therefore the claim

3, 4, and 6 may be further limiting to "administering" only. However, "further comprising" is suggestive of additional steps. Therefore, it is unclear if the intent of claims 3, 4, and 6 are to further limit the claims or to add additions steps. Therefore, the metes and bounds are unclear.

Claim 5 is dependent from claim 4, which has been deemed indefinite; therefore, claim 5 is rendered indefinite.

Claims 9, 10, 11, and 13 recite, "further comprising". The term "further comprising" in reference to a product suggests that additional components are being added to the composition of the product. However, in the instant claims no additional components are added.

Claim 12 is dependent from claim 11, which has been deemed indefinite; therefore, claim 12 is rendered indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1 and 3-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsuji et al. (1995; of record).

The claimed invention is drawn to a method comprising: (1) transfecting cell of an affected tissue with a nucleic acid encoding AOP-1 or a nucleic acid encoding a

polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 or (2) administering a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1. The instant invention is also drawn to a prophylactic or therapeutic agent comprising (1) a nucleic acid encoding AOP-1 or a nucleic acid encoding a polypeptide having an addition, deletion, or substitution of one or more amino acids as compare to with the amino acid sequence of AOP-1 while retaining the function of AOP-1 or (2) a material enhancing the expression of AOP-1 gene, the production of AOP-1, or the function of AOP-1.

Tsuji et al discloses cDNA sequences and an expression system that encode human and mouse Mer5 cDNA and mutation of Mer5 gene sequence. Mer5 is also disclosed to be the AOP-1 gene (see abstract, Figure 1 on page 379, and par bridging p. 379 and 380). Tsuji et al also discloses methods for making Mer5 nucleic acid sequences with a mutation to encode mutant Mer5 proteins and method of transfecting *E. coli* lacking function *aphC*, a gene involved in antioxidant activities (see Materials and Methods, p. 377). Tsuji et al also disclose the expression of AOP-1 gene product in E. coli deficient in the C22-subunit gene rescued resistance of the bacteria to alkylhydroperoxide (see abstract).

Because the instant claims do not specify the subject that is to be transfected or the specific vector to be used, the E. Coli transfected with the mammalian AOP-1 vector encompasses the limitations of the claims. The instant treatment of E. coli with the AOP-1 gene results in the rescue of antioxidant activities lost by a mutation in the *aphC*

gene of the treated *E. coli*. Therefore, the disclosed vector encoding AOP-1 and the method of transfection encompass a therapeutic agent and treatment as claimed.

Because claims 7 and 14 do not change the method steps or the composition of claim 1 and 8 from which they depend, the claims were deemed to be duplicate claims of 1 and 8 (see Double Patenting above). Since claims 1 and 8 are anticipated by the instant art, the duplicate claims 7 and 18 are also anticipated by the Tsuji et al.

Relevant Art

11. In a post-filing art, Applicants demonstrate the protective effects of AOP-1 overexpression in transgenic mice. Overexpression of AOP-1 inhibited left ventricular remodeling and failure after myocardial infarction in transgenic mice overexpressing AOP-1 (Matsushima et al. Circulation 113:1779-1786, 2006).

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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